

WHAT IS CLAIMED IS:

1 1. A method for identifying a ligand for a receptor comprising the
2 steps of:

- 3 a) providing a substrate comprising an adsorbent wherein the
4 receptor is bound to the adsorbent;
5 b) exposing the bound receptor to a sample containing the ligand
6 under conditions to allow binding between the receptor and the ligand; and
7 c) detecting bound ligand by desorption spectrometry.

1 2. A method of detecting a genetic package containing a
2 polynucleotide that encodes a polypeptide agent that specifically binds to a target
3 adsorbent, the method comprising the steps of:

- 4 a) providing a substrate comprising a target adsorbent;
5 b) providing a display library that comprises a plurality of different
6 genetic packages, each different genetic package comprising a polynucleotide that
7 comprises a nucleotide sequence that encodes a polypeptide agent, and each different
8 genetic package having a surface on which the encoded polypeptide agent is displayed;
9 c) exposing the substrate to the display library under elution
10 conditions to allow specific binding between a polypeptide agent and the target adsorbent,
11 whereby a genetic package comprising the polypeptide agent is retained on the substrate;
12 and
13 d) detecting a genetic package retained on the substrate by
14 desorption spectrometry.

1 3. The method of claim 2 wherein the display library is a phage
2 display library.

1 4. The method of claim 2 wherein the step of providing the substrate
2 comprising the target adsorbent comprises the steps of:

- 3 i) providing a substrate comprising an adsorbent, wherein
4 the adsorbent retains a target analyte under an elution condition; and

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5 ii) exposing the adsorbent to the target analyte under the
6 elution condition to allow retention of the target analyte by the adsorbent, whereby the
7 target analyte becomes the target adsorbent.

1 5. The method of claim 2 further comprising the step of (e)
2 sequencing the nucleotide sequence that encodes the polypeptide agent.

1 6. The method of claim 2 further comprising the step of (e) isolating
2 the retained genetic package.

1 7. The method of claim 2 further comprising the step of (e) producing
2 the polypeptide agent.

1 8. The method of claim 2 wherein the substrate comprises (1) an
2 adsorbent that binds an anchoring polypeptide and (2) at least one target genetic package
3 having a surface displaying the anchoring polypeptide and a target adsorbent polypeptide,
4 the target genetic package comprising a polynucleotide that comprises a nucleotide
5 sequence that encodes the target adsorbent, wherein the target genetic package is bound
6 to the adsorbent through the anchoring polypeptide.

1 9. The method of claim 2 wherein the substrate comprises a cell or
2 cell membrane.

1 10. The method of claim 2 wherein the target adsorbent comprises a
2 polypeptide that is differentially expressed between cells of different phenotypes.

1 11. The method of claim 3 wherein the phage is M13.

1 12. The method of claim 4 wherein the target analyte is a target
2 polypeptide and the step of ii) exposing the adsorbent comprises the step of producing the
3 target polypeptide *in situ* on the adsorbent by *in vitro* translation of a polynucleotide
4 encoding the target polypeptide.

1 13. The method of claim 5 wherein the step of sequencing comprises
2 amplifying the polynucleotide sequence *in situ* on the substrate.

1 14. The method of claim 7 wherein the step of producing comprises
2 reproducing the retained genetic package that displays the polypeptide agent.

1 15. The method of claim 7 comprising expressing the polypeptide agent
2 from an expression vector that comprises an expression control sequence operatively
3 linked to the nucleotide sequence encoding the polypeptide agent.

1 16. The method of claim 7 further comprising the step of producing a
2 substrate comprising an adsorbent that comprises the polypeptide agent.

1 17. The method of claim 8 wherein the at least one target genetic
2 package is selected from a target display library screened for genetic packages that bind
3 at least one primary target analyte and wherein the adsorbent comprises the primary
4 target analyte.

1 18. The method of claim 11 wherein the polypeptide agent is a single
2 chain antibody.

1 19. The method of claim 12 wherein the target polypeptide is produced
2 *in situ* by *in vitro* translation of a polynucleotide encoding the target polypeptide.

1 20. The method of claim 14 wherein the step of reproducing is carried
2 out *in situ* on the substrate.

1 21. The method of claim 19 wherein the polynucleotide encoding the
2 target polypeptide is produced *in situ* by *in vitro* transcription.

3 22. A substrate for desorption spectrometry comprising an adsorbent
4 that binds an anchoring polypeptide displayed on a surface of a genetic package, wherein
5 the surface of the genetic package further displays a target polypeptide and wherein the

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genetic package comprises a polynucleotide comprising a nucleotide sequence that encodes the target polypeptide.

23. The substrate of claim 22 wherein the genetic package is an M13 phage.

24. The substrate of claim 22 wherein the anchoring polypeptide is a fusion polypeptide with gene III protein and the target polypeptide is a fusion polypeptide with gene VIII protein.

25. A substrate comprising an adsorbent that comprises a polypeptide agent that specifically binds to a target analyte, the polypeptide agent identified by the method of claim 33.

26. The substrate of claim 25 wherein the polypeptide agent is a single chain antibody.

27. A method for detecting translation of a polynucleotide comprising the steps of:

a) providing a substrate comprising an adsorbent for use in desorption spectrometry;

b) contacting the substrate with the polynucleotide encoding a polypeptide and with agents for *in vitro* translation of the polynucleotide, whereby the polypeptide is produced;

c) exposing the substrate to an eluant to allow retention of the polypeptide by the adsorbent; and

d) detecting retained polypeptide by desorption spectrometry; whereby detection of the polypeptide provides detection of translation of the polynucleotide.

28. A method comprising the steps of:

a) exposing a first sample to a primary adsorbent and to an eluant to allow retention of a first analyte by the adsorbent, and detecting the adsorbed analyte

4 by desorption spectrometry, whereby the retained first analyte becomes a secondary
5 adsorbent;

6 b) exposing a second sample to the secondary adsorbent and to an
7 eluant to allow retention of a second analyte by the secondary adsorbent, and detecting
8 the adsorbed second analyte by desorption spectrometry, whereby the retained second
9 analyte becomes a tertiary adsorbent.

1 29. The method of claim 28 further comprising repeating step (b) at
2 least once for a subsequent sample or samples.

1 ~~Sub By~~ 30. A screening method for determining whether an agent modulates
2 binding between a target analyte and an adsorbent comprising the steps of:

3 a) providing a substrate comprising an adsorbent to which the target
4 analyte binds under an elution condition;

5 b) exposing the substrate to the target analyte and to the agent
6 under the elution condition to allow binding between the target analyte and the adsorbent;

7 c) detecting an amount of binding between the target analyte and
8 the adsorbent by desorption spectrometry; and

9 d) determining whether the measured amount is different than a
10 control amount of binding when the substrate is exposed to the target analyte under the
11 elution condition without the agent;

12 whereby a difference between the measured amount and the control
13 amount indicates that the agent modulates binding.

1 31. The method of claim 30 wherein the adsorbent comprises a ligand
2 that specifically binds the target analyte.

1 32. The method of claim 30 wherein the adsorbent comprises a genetic
2 package having a surface that displays a polypeptide ligand that specifically binds the
3 target analyte.

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1 ~~ABs~~ 33. The method of claim 30 for screening a combinatorial library of
2 agents comprising exposing each of a plurality of agents in the library to each of a
3 plurality of the adsorbents.

1 34. The method of claim 31 wherein the ligand is an enzyme and the
2 target analyte is a substrate of, or an inhibitor for, the enzyme, or vice-versa.

1 35. The method of claim 31 wherein the ligand is a hormone and the
2 target analyte is a cell surface receptor or an intracellular receptor of the hormone, or
3 vice-versa.

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